

### **Remarks**

The specification has been amended to update the status of related applications and to correct the citation of trademarks. Applicants have provided a generic term for INACTINE<sup>TM</sup> as required by the Examiner. Support for this amendment can be found in U.S. Patent No. 6,093,564 B1 (col. 5, lines 59-61), the entire contents of which are incorporated by reference in the instant specification (page 7, lines 5-9). Applicants have also capitalized and provided a generic term for DiffQuick, although Applicants have no evidence that this term is indeed a trademark.

Claims 7, 8, 20-30 and 32-34 are cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of cancelled claims in a continuing application.

Claims 1, 2, 6, 10, 12, 17, 18 and 31 are amended. Claim 1 is amended to add the limitations of claims 7 and 8. Support for this amendment is found in claims 7 and 8 as originally filed and in the specification at least on page 2, line 33 and page 3, line 1. Claim 2 is amended to add the phrase "the group consisting of" to recite correct Markush group claim language. Claim 6 is amended to delete the term "comprises" and replace it with the term "is". Claim 10 is amended to correct its dependency from claim 6 to claim 9. Claim 12 is amended to correct its dependency from claim 8 to claim 11. Claims 17 and 18 are amended to recite terms with correct antecedent basis. Claim 31 is amended to correct a typographical error. As a result, claims 1-6, 9-19 and 31 are pending for examination with claim 1 being an independent claim.

No new matter has been added.

### **Restriction Requirement**

Applicants affirm the oral election of Group I (claims 1-19 and 31, drawn to a method for selectively inactivating a parasite in a biological composition) made by John Van Amsterdam on April 28, 2004. Claims 20-30 and 32-34 are cancelled herewith. Applicants reserve the right to pursue the subject matter of non-elected claims in a continuing application.

### **Priority**

The Examiner has indicated that claims 1-8, 12-13, 16-19 and 31 are entitled to a priority date of August 29, 1995 and claims 9-11 and 14-15 are entitled to a priority date of May 13,

1997. Applicants wish to point out that the August 29, 1995 priority document discloses species which fall within the formula of currently pending claims 9 and 11.

The Examiner requested that the priority claim be updated to include Application No. 10/406,875, filed April 4, 2003. However, Applicants have reviewed and updated the priority claim and consider it correct without reference to this application. The Examiner is asked to clarify her request, if still necessary in view of the arguments presented herein.

### **Specification Objection**

The specification is objected to because of the use of trademarks INACTINE™ and DiffQuick.

The trademark INACTINE™ is defined in U.S. Patent No. 6,093,564 B1 (incorporated by reference on page 7, lines 5-9) as “compounds ... having (1) an aziridino moiety or a halo-hydrocarbon-amine moiety, and (2) two or more nitrogen atoms separated by hydrocarbon moieties.” Applicants have amended the first recitation of this trademark in the specification to include this description.

DiffQuick is a cell staining solution containing thiazine and eosin. There is no evidence to show that the term is a trademark. However in the interest of expediting prosecution, Applicants have amended the specification to capitalize this term and add this description.

Accordingly, withdrawal of this objection to the specification is respectfully requested.

### **Claim Objections**

Claims 2, 6 and 10 are objected to for the following reasons. Claim 2 is objected to as containing an improper Markush group. Applicants have amended the claim to add the phrase “the group consisting of”. Claim 6 is objected to as failing to further limit claim 2. Applicants have amended claim 6 to replace “comprises” with “is”. Claim 10 is objected to for failing to further limit the subject matter of a previous claim. Applicants have amended claim 10 to depend from claim 9.

Accordingly, withdrawal of the objections to the claims is respectfully requested.

**Double Patenting Rejection**

**U.S. Application No. 10/406,875**

Claims 1-6 and 8-12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of co-pending U.S. Application No. 10/406,875, now U.S. PreGrant Publication 2003/0202986.

Applicants have amended claim 1 to include the limitation of claim 7, which was not rejected in view of 10/406,875. Claims 1-6 and 8-12 therefore should be patentable in view of 10/406,875. Applicants do not otherwise concede to the propriety of the Examiner's comments.

Accordingly, withdrawal of this rejection is respectfully requested.

**U.S. Patent No. 6,093,564**

Claims 1-6 and 8-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,093,564.

Applicants have amended claim 1 to add the limitation of claim 7, which was not rejected in view of 6,093,564. Claims 1-6 and 8-12 therefore should be patentable in view of 6,093,564. Applicants do not otherwise concede to the propriety of the Examiner's comments.

Accordingly, withdrawal of this rejection is respectfully requested.

**U.S. Patent No. 6,352,695**

Claims 1-6 and 8-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,352,695.

Applicants have amended claim 1 to add the limitation of claim 7, which was not rejected in view of 6,352,695. Claims 1-6 and 8-12 therefore should be patentable in view of 6,352,695. Applicants do not otherwise concede to the propriety of the Examiner's comments.

Accordingly, withdrawal of this rejection is respectfully requested.

**U.S. Application No. 09/877,838**

Claims 1-4, 14, 17 and 19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 and 7-10 of U.S. Application 09/877,838, now U.S. PreGrant Publication 2002/0034724.

Applicants have amended claim 1 to add the limitation of claim 7, which was not rejected in view of 09/877,838. Claims 1-4, 14, 17 and 19 therefore should be patentable in view of 09/877,838. Applicants do not otherwise concede to the propriety of the Examiner's comments.

Accordingly, withdrawal of this rejection is respectfully requested.

**Rejection under 35 U.S.C. §112, second paragraph**

Claims 1-19 and 31 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner considers the claims indefinite due to the recitation of "selectively inactivating" (claim 1), "n/-W" and "inclusive" (claim 9), "inclusive" and "counter anion" (claim 11), and "contacting the biological composition with parasiticide" (claim 31).

The term "selectively inactivating" in claim 1 is found within the specification at least on page 17, lines 15-27 and page 21, lines 1-4. The specification defines "inactivating" to mean "diminishing or eliminating the number of infectious parasites measured as a decrease in the infectious titer or number of infectious parasites per volume (e.g., per ml of a treated biological composition)". (See page 20, lines 20-25.) "Selective" is given its ordinary meaning (i.e., ability to choose, distinguish or differentiate). With respect to parasites in biological compositions, selective inactivation means that parasites are targeted by the compounds of the invention more so than are other components of the biological composition.

The term "n/-W" in claim 11 is a quotient that represents the number of counter anions that are required to charge neutralize the compound (i.e., n divided by -W). W and n are described in the claims and the specification. As W represents the valency of the counter anion it is expected to be a negative number inherently.

The term "inclusive" in claims 9 and 11 has its ordinary meaning and is a term understood by one of ordinary skill in the art. The phrase "between two and four carbon atoms, inclusive" as recited in claims 9 and 11 would be understood by one of ordinary skill in the art to mean two carbon atoms, three carbon atoms or four carbon atoms. The phrase "between one and four carbon atoms, inclusive" as recited in claims 9 and 11 means one carbon atom, two carbon

atoms, three carbon atoms or four carbon atoms. The phrase “between one and ten, inclusive” as recited in claims 9 and 11 means one, two, three, four, five, six, seven, eight, nine or ten.

The term “counter anion” in claim 11 has its ordinary meaning in the art (i.e., an ion having a negative charge that is paired with a respective cation). The specification provides examples of suitable counter anions such as nitrate, sulfate, halide (fluorine, chlorine, bromine, iodine), phosphate and tosylate ions (page 8, lines 18-19).

The phrase “contacting the biological composition with parasiticide” in claim 31 has its ordinary meaning (i.e., bringing the biological composition into physical association with a parasiticide). Contacting can be achieved by methods known to those of ordinary skill in the art (e.g., by incubation, as described on page 18, lines 12-21). Biological composition is defined on page 19, lines 21-33. Parasiticides are defined and examples thereof are provided on page 16, lines 6-19. Claim 31 is also amended to place “a” before parasiticide.

In view of the foregoing, claims 1-19 and 31 are considered definite.

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

#### **Rejection under 35 U.S.C. §102**

##### **Cook et al. (U.S. Patent No. 6,410,219)**

Claims 1-7 and 31 are rejected under 35 U.S.C. §102(e) as being anticipated by Cook et al. (U.S. Patent No. 6,410,219). According to the Examiner, Cook et al. “teach a method of inactivating pathogens in human blood products ... comprising adding a compound having a mustard group ... and a nucleic acid binding ligand comprising a acridine group ... to a blood product comprising red blood cells suspected of containing pathogens.” The Examiner asserts that a compound having a mustard group is inherently a parasiticide and “is believed to form reactive intermediates such as aziridinium or aziridino complexes.”

Applicants have amended claim 1 to include the limitation that the aziridino compound contains a linear alkyl group as recited in claim 8, which was not rejected in view of Cook et al. The claims as amended therefore are not anticipated by Cook et al.

Accordingly, withdrawal of this rejection is respectfully requested.

Vial et al. (Biochemical. Pharmacol., 1984, 39(17):2761-2770)

Claims 1-3, 7 and 17-19 are rejected under 35 U.S.C. §102(b) as being anticipated by Vial et al. (Biochemical. Pharmacol., 1984, 39(17):2761-2770). According to the Examiner, Vial et al. "teach erythrocytes parasitized by *P. falciparum* cultivation in AB<sup>+</sup> human erythrocytes in complete medium suspensions containing AB<sup>+</sup> serum drug effects, e.g. aziridino ethanol (inherently an aziridino compound) on parasitic growth assays."

Applicants have amended claim 1 to include the limitation that the aziridino compound contains a linear alkyl group as recited in claim 8, which was not rejected in view of Vial et al. The claims as amended therefore are not anticipated by Vial et al.

Accordingly, withdrawal of this rejection is respectfully requested.

**Rejection under 35 U.S.C. §103(a)**

Claims 1-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Vial et al. (Biochemical. Pharmacol., 1984, 39(17):2761-2770) in view of Christianson et al. (J. Clin. Microbiol., 1980, 11(4):377-379). According to the Examiner, "it would have been prima facie obvious ... to combine/substitute the aziridino compounds of Christianson et al. in the method of Vial et al. with the expectation of increasing the inactivation of parasites, e.g., *Plasmodium* in biological compositions because Vial et al. teach that this first attempt to define relationships between the certain structural features of the drugs tested i.e. aziridino compounds and their inhibitory effect of the growth of *P. falciparum* *in vitro* should be extremely useful for the design of future structural analogs."

The claimed invention is not rendered obvious by the combination of Vial et al. and Christianson et al. because there is no motivation to combine the references and no reasonable expectation that such combination would be successful. Therefore combination of the references is improper. Notwithstanding this, even if the references could be combined, the combination does not provide each and every limitation of the claims as now amended.

Christianson et al. attempts to identify a compound useful in inactivating serum contaminants such as viruses and mycoplasma, in order to produce a contaminant-free serum for *in vitro* cell culture. The reference analyzes the ability of a monomeric binary ethyleneimine (BEI) compound lacking an alkyl group to inactivate mycoplasma. It concludes that the

compound should not be used for this purpose. (See page 379, first column, "Therefore, treatment of serum with BEI to rid it of mycoplasma cannot be recommended by the results of these tests.") Christianson et al. further reports bacterial contamination in all vials exposed to the BEI compound, leading the authors to question the compound's efficacy in bacterial inactivation.

Vial et al., which published four years after Christianson et al., studied the anti-Plasmodium activity of known compounds to identify a therapeutic anti-malarial drug. The set of compounds tested did not include BEI, even though that compound would have been known and available to Vial et al. at the time. Instead Vial et al. focuses on polar head group containing compounds because it sought a compound that would interfere with phospholipid metabolism, which was known to be critical for Plasmodium infection. Vial et al. reports that polar head group phospholipid analogs, such as aziridine ethanol, inhibited Plasmodium growth. Vial et al. also reports that increasing chain length between the nitrogen and hydroxyl groups in such compounds reduced anti-Plasmodium activity, thereby discouraging chain lengths longer than three methylene groups. Vial et al. concludes that the IC<sub>50</sub> values of the tested compounds were not therapeutically practical and then suggests the design and testing of new polar head group containing compounds.

Without a motivation to combine and a reasonable expectation of success (as discussed below), it is improper to combine the references. However, even if such combination was proper, the combination would not produce the claimed invention. The combination does not result in aziridino compounds having a linear alkyl group at least because neither reference teaches such compounds, as evidenced at least by the novelty rejections presented by the Examiner. Additionally, there is nothing in either reference to modify compounds towards those of the pending claims. For example, Christianson et al. altogether teaches away from BEI as an anti-mycoplasma agent and Vial et al. teaches away from compounds with increasing chain length between the ringed nitrogen and the end of the molecule. Therefore, the combination does not provide each and every element of the pending claims.

There is no motivation to use the Christianson et al. compound in the assay of Vial et al. at least because the aim of the two papers is different. Christianson et al. is directed to inactivating mycoplasma in serum to be used in cell culture. Vial et al. is directed to identifying an anti-parasite compound for therapeutic use in vivo. Mycoplasma are not parasites and in vitro

and in vivo assay requirements and tolerances are not necessarily consistent. There is also no motivation to combine the references because their teachings are either inconsistent or at least do not lead towards each other. Vial et al. teaches that polar head group compounds can inhibit Plasmodium. Vial et al. did not study the BEI compound of Christianson et al. even though it was undoubtedly available, presumably because the BEI compound lacked the requisite polar head group. Regardless, Christianson et al. teaches away from the use of the BEI compound for inactivating mycoplasma contamination, and questions whether the compound has any anti-bacterial activity. For at least these reasons, there would be no motivation to use the BEI compound of Christianson et al. in the methods of Vial et al.

There is no reasonable expectation of success that the compound of Christianson et al. would function in the Plasmodium inactivation assay of Vial et al. As stated above, Christianson et al. teaches away from the use of the BEI compound in mycoplasma inactivation due to its unreliable and impractical nature, and it further calls into question the compound's efficacy in bacterial inactivation. Vial et al. teach that compounds useful for Plasmodium inactivation should have a polar head group; the BEI compound of Christianson et al. lacks such a group. Therefore, there is no reasonable expectation that the BEI compound would inactivate Plasmodium based on the teachings of the references.

In view of the foregoing, the claimed invention therefore is not rendered obvious by Vial et al. in view of Christianson et al.

Accordingly, withdrawal of this rejection is respectfully requested.

**Conclusion**

The claims are now considered in condition for allowance and a notice to that effect is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,  
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Docket No.: V0191.70030US00  
Date: November 9, 2004  
x11/09/04x